Remarks

The present Amendment amends the specification on pages 1, 2, 3, 4, 9, 10, 13, 71 and 76 in order to correct several typographical errors. In regard to the claims, Applicant has cancelled without prejudice claims 1-41, and has added new claims 42-69. The new claims are supported by the teachings in the specification. Applicant has also requested that the Patent Office change their office records to reflect the new docket number for this matter on all future communications.

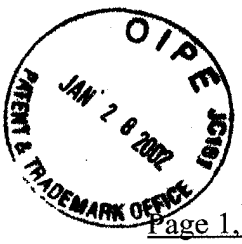
Applicant submits that no new matter is entered by this Preliminary Amendment and respectfully requests entry of the Amendment and allowance of the claims. Although no fee is believed due, the Commissioner is hereby authorized to charge any fees which may be required by submission of this Preliminary Amendment to Deposit Account No. 50-0951.

Respectfully submitted,

AKERMAN, SENTERFITT & EIDSON, P.A.

Dated: 12/14/01

Gregory A. Nelson
Registration No. 30,577
Neil R. Jetter
Registration No. 46,803
P.O. Box 3188
West Palm Beach, FL 33402-3188
Tel: 561-653-5000



MARKED-UP VERSION OF SPECIFICATION SHOWING CHANGES

Page 1, line 14:

This present invention provides an advanced mutifunctional biochip (AMB) that [combine] combines integrated circuit elements, electro-optical excitation and detection systems, and molecular receptor probes in a self-contained integrated microdevice. Methods for the use of such devices in the detection and quantitation of biomolecules, and their application to diagnostic and therapeutic regimens are also provided.

Page 2, lines 27 and 30:

One type of devices, often referred to as a "biochip" combines semiconductor detection system with biotechnology-based probes, and has received increasing interest. The inventor has developed a variety of self-contained biochip devices and systems (*e.g.,* U. S. Pat. Appl. Ser. No. 08/979,672, filed Nov. 26, 1997; Intl. Pat. Appl. Ser. No. PCT/US98/25294, filed Nov. 25, 1998, and U. S. Pat. Appl. Ser. No. 09/236,758, filed Jan. 25, 1999, the entire contents of each of which is incorporated herein by reference in its entirety). While such biochips (as well as other currently available biochip devices) have several detection channels, they are, however, designed to use only one specific type of bioreceptor at a time, and are therefore unsuitable for simultaneous multidetection of a plurality of [species] diverse biotargets. While these earlier biochip systems may be used for detecting either an individual or a plurality of a particular biochemical species on a single chip at the same time (*e.g.,* in detecting one or more polynucleotides or in detecting one or more polypeptides, they were not devised to detect multiple diverse biochemical species at the same time on the same chip (*i.e.* the simultaneous detection of polypeptides and polynucleotides on a single chip).

Page 3, lines 18 and 24:

There is a critical demand for a rapid, simple, cost-effective technique for screening samples, such as blood or other clinical samples, for the presence of biomolecules (including polynucleotides, polypeptides, *etc.*) to assist in the diagnosis and treatment of medical diseases, including those caused by infectious pathogens, and the like, as well as provide efficient means for quantitating such molecules in pathology and forensics samples. The development of inexpensive screening analyses that would permit simultaneous analyses of multiple [biological molecules] diverse biotargets would allow rapid detection and improved treatments of many illnesses, facilitate improvements in quality control and manufacturing, as well as provide rapid, affordable devices for detection of biomolecules in the areas of environmental contamination and remediation processes.

The development of rapid and effective screening tests for simultaneous assay of two or more different types of molecules (*e.g.*, detecting antibodies and polynucleotides in a [samples] sample on a single biochip) would also reduce the cost of diagnostic testing services, biochemical analyses and assay systems, as well as overall costs in the health care industry. For example, a critical factor in medical diagnostics is rapid, selective, and sensitive detection of biochemical substances (protein, metabolites, nucleic acids), biological species or living systems (bacteria, virus or related components) at ultra-trace levels in biological samples (*e.g.*, tissues, blood and other bodily fluids). To achieve the required level of sensitivity and specificity in detection, it is often necessary to use a biosensor that is capable to identify and differentiate a large number of biochemical constituents in complex samples. The development of a cost-effective biochip alternative to simultaneous quantitation of pluralities of differing biological molecules would be a revolutionary advance in the fields of analytical chemistry and medicine.

Page 4, lines 22 and 27:

There is also a distinct need for development of advanced multifunctional devices that permit the rapid, large-scale and cost effective analysis of pluralities of heterogeneous macromolecules, and permit the development of methods for detecting and quantitating multiple [molecular species] diverse biotargets in mixed biological samples.

2.0 SUMMARY OF THE INVENTION

This present invention overcomes these and other limitations in the prior art by providing for the first time, an advanced multifunctional biochip (AMB) that is capable of simultaneous detection of two or more [different biological macromolecules] diverse macromolecule biotargets (or "targets"). These macromolecules may comprise a plurality of polynucleotides (including DNAs, PNAs and/or RNAs), a plurality of polypeptides, peptides, and/or proteins; a plurality of enzymes, antibodies, and/or receptors or antigens); a plurality of pathogens, organisms, microorganisms, and/or viruses, *etc.*); or a plurality of cells, cell types, tissues, organelles, organs, fluids, and/or other intracellular or extracellular components of a living cell. Alternatively, the biological macromolecules may be a combination of any of these or other biological compounds that may be detected using an AMB that comprises a plurality of receptor probes, or biomimetic probes on a single device. Such design permits the simultaneous or sequential detection of a variety of targets using a single biochip device, and as such provides methods of detecting and quantitating a number of diverse biochemical compounds using a single device.

Page 9, lines 5, 11 and 16:

The inventor and others have developed two types of biochips, one using phototransistors (Vo-Dinh *et al.*, 1998a; 1998b) and the other using photodiode systems (Vo-Dinh, 1998a; 1998b). Exemplary biochip IC systems based on photodiode circuitry typically comprise 16 channels (*e.g.,* in a 4 ´ 4 array), or larger (*e.g.,* a 100-channel system that comprises a 10 x 10 array). The biochips include a large-area, [e-well] n-well integrated amplifier-photodiode array that has been designed as a single, custom integrated circuit (IC), fabricated for the biochip. This IC device is coupled to the multiarray sampling platform and is designed for monitoring very low light levels. The individual photodiodes have 900-mm square size and are arrayed on a 1-mm spacing grid. The photodiodes and the accompanying electronic circuitry were fabricated using a standard 1.2-micron [e-well] n-well CMOS process. The use of this type of standard process allows the production of photodiodes and phototransistors as well as other numerous types of analog and digital circuitry in a single IC chip. This feature is the main advantage of the CMOS

technology in comparison to other detector technologies such as charge-coupled devices or charge-injection devices. The photodiodes themselves are produced using the [e-well] n-well structure that is generally used to make resistors or as the body material for transistors. Since the anode of the diode is the p-type substrate material, which is common to every circuit on the IC chip, only the cathode is available for monitoring the photocurrent and the photodiode is constrained to operate with a reverse bias.

Page 10, line 34:

The target nucleic acid may be immobilized onto the integrated microchip that also supports a phototransducer and related detection circuitry. Alternatively, a gene probe may be immobilized onto a membrane or filter that is then attached to the microchip or to the detector surface itself. This approach avoids the need to bind the bioreceptor directly to the transducer and thus is attractive for simplifying large-scale production.

Page 13, lines 14 and 22:

FIG. 8 illustrates schematically the integration of multiple AMB devices for high throughput screening of large numbers of samples. Shown is a 10 × 10 array of biochips that can provide [100,000] 10,000 (10^4) sensing channels.

4.0 DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

4.1 SOME ADVANTAGES OF THE INVENTION

The advanced multifunctional biochip system of the present invention offers a unique combination of performance capabilities and analytical features of merit not available in any other analysis system currently available. With its multichannel and multifunctional capabilities, the advanced biochip technology is the only current system that allows simultaneous detection of multiple diverse biomolecular targets simultaneously. The AMB devices of the present invention find utility in a wide variety of applications, and particularly in the areas of medical diagnostics, gene identification, and mapping, polynucleotide sequencing, environmental bioremediation, and related biotechnology applications.

Page 71, line 21:

Hybridization occurs between complementary DNA sequences and binding antibody-antigen was demonstrated by the fluorescence signals detected by the biochip. FIG. 4 shows that only fluorescence signals were detected on the biochip channels where hybridization of labeled DNA HIV1 (TB) gene probes with complementary bound-DNA fragments had occurred. This figure shows the simultaneous detection of HIV, TB and Goat IgG protein using HIV DNA probe (4 channels corresponding to the first row of the biochip), TB DNA probe (second row), and antibody probe for Goat IgG (fourth row). The blank signals (which correspond to DNA that is not complementary to the probes, or antigens not targeted by the antibody probes) are shown in the third row for comparison. The results demonstrate the use of the multifunctional biochip to detect more than one diverse biotarget type of macromolecule on a single chip device.

Page 76, line 28:

5.7 EXAMPLE 7 - HIGH-THROUGHPUT SCREENING AMB SYSTEM

Integration of multiple biochips (for example 10 × 10 will provide [100,000] 10,000 (10^4) sensing channels for high throughput screening (FIG. 8). With its multichannel capability, the AMB technology is the only current system that allows simultaneous detection of multiple medical targets (up to 100 channels) simultaneously using antibody, DNA, as well as other bioreceptors (proteins, cells, biomimetic systems).